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(54) Title: SUBSTITUTED PHENETHYLSULFONES AND METHOD OF REDUCING TNF α LEVELS (57) Abstract Phenethylsulfones substituted α to the phenyl group with a 1-oxoisindoline or 1,3-dioxoisindoline reduce the levels of TNF α in a mammal. A typical embodiment is 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisindoline-1,3-dione.		

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***SUBSTITUTED PHENETHYLSULFONES AND
METHOD OF REDUCING TNF α LEVELS***

The present invention relates to substituted phenethylsulfones substituted α to the phenyl group with a 1-oxoisindoline group, the method of reducing levels of tumor necrosis factor α and treating inflammatory and autoimmune diseases in a mammal through the administration thereof, and to pharmaceutical compositions of such derivatives.

Background of the Invention

Tumor necrosis factor α , or TNF α , is a cytokine which is released primarily by mononuclear phagocytes in response to a number immunostimulators. When administered to animals or humans, it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states. Excessive or unregulated TNF α production thus has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome {Tracey *et al.*, *Nature* 330, 662-664 (1987) and Hinshaw *et al.*, *Circ. Shock* 30, 279-292 (1990)}; rheumatoid arthritis, Crohn's disease, IBD, cachexia {Dezube *et al.*, *Lancet*, 335 (8690), 662 (1990)} and Adult Respiratory Distress Syndrome where TNF α concentration in excess of 12,000 pg/mL have been detected in pulmonary aspirates from ARDS patients {Millar *et al.*, *Lancet* 2(8665), 712-714 (1989)}. Systemic infusion of recombinant TNF α also resulted in changes typically seen in ARDS {Ferrai-Baliviera *et al.*, *Arch. Surg.* 124(12), 1400-1405 (1989)}.

TNF α appears to be involved in bone resorption diseases, including arthritis. When activated, leukocytes will produce bone-resorption, an activity to which the data suggest TNF α contributes. {Bertolini *et al.*, *Nature* 319, 516-518 (1986) and Johnson *et*

al., *Endocrinology* 124(3), 1424-1427 (1989)}. TNF α also has been shown to stimulate bone resorption and inhibit bone formation *in vitro* and *in vivo* through stimulation of osteoblast formation and activation combined with inhibition of osteoblast function. Although TNF α may be involved in many bone resorption diseases, including arthritis,
5 a most compelling link with disease is the association between production of TNF α by tumor or host tissues and malignancy associated hypercalcemia {*Calci. Tissue Int. (US)* 46(Suppl.), S3-10 (1990)}. In Graft versus Host Reaction, increased serum TNF α levels have been associated with major complication following acute allogenic bone marrow transplants {Holler *et al.*, *Blood*, 75(4), 1011-1016 (1990)}.

10 Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNF α and the most severe complication occurring in malaria patients. Levels of serum TNF α correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks {Grau *et al.*, *N. Engl. J. Med.* 320(24), 1586-1591 (1989)}.

15 Macrophage-induced angiogenesis is known to be mediated by TNF α . Leibovich *et al.* {*Nature*, 329, 630-632 (1987)} showed TNF α induces *in vivo* capillary blood vessel formation in the rat cornea and the developing chick chorioallantoic membranes at very low doses and suggest TNF α is a candidate for inducing angiogenesis in inflammation, wound repair, and tumor growth. TNF α production also has been associated with
20 cancerous conditions, particularly induced tumors {Ching *et al.*, *Brit. J. Cancer*, (1955) 72, 339-343, and Koch, *Progress in Medicinal Chemistry*, 22, 166-242 (1985)}.

TNF α also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNF α completely blocked the silica-

induced lung fibrosis in mice {Pignet *et al.*, *Nature*, 344:245-247 (1990)}. High levels of TNF α production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette *et al.*, *Inflammation* 13(3), 329-339 (1989)}. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNF α as compared with macrophages from normal donors {Baughman *et al.*, *J. Lab. Clin. Med.* 115(1), 36-42 (1990)}.

TNF α is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder *et al.*, *PNAS* 87, 2643-2646 (1990)}. TNF α also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry *et al.*, *J. Cell Biol.* 107, 1269-1277 (1988)}. TNF α has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF α -induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro *et al.*, *Am. J Path.* 135(1), 121-132 (1989)}.

TNF α blockage with monoclonal anti-TNF α antibodies has been shown to be beneficial in rheumatoid arthritis {Elliot *et al.*, *Int. J. Pharmac.* 1995 17(2), 141-145} and Crohn's disease {von Dullemen *et al.*, *Gastroenterology*, 1995 109(1), 129-135}

Moreover, it now is known that $\text{TNF}\alpha$ is a potent activator of retrovirus replication including activation of HIV-1. {Duh *et al.*, *Proc. Nat. Acad. Sci.* 86, 5974-5978 (1989); Poll *et al.*, *Proc. Nat. Acad. Sci.* 87, 782-785 (1990); Monto *et al.*, *Blood* 79, 2670 (1990); Clouse *et al.*, *J. Immunol.* 142, 431-438 (1989); Poll *et al.*, *AIDS Res. Hum. Retrovirus*, 191-197 (1992)}. AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified; *i.e.*, HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically $\text{TNF}\alpha$, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably $\text{TNF}\alpha$, in an HIV-infected individual assists in limiting the maintenance of T lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, also have been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. {Rosenberg *et al.*, *The Immunopathogenesis of HIV Infection*, *Advances in Immunology*, 57 (1989)}. Cytokines, such as $\text{TNF}\alpha$, have been shown to activate HIV replication in monocytes and/or macrophages {Poli *et al.*, *Proc.*

Natl. Acad. Sci., 87, 782-784 (1990)); therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression for T cells. Additional studies have identified TNF α as a common factor in the activation of HIV *in vitro* and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, *et al.*, *PNAS* 86 2336-2340). This evidence suggests that a reduction of TNF α synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNF α {Folks *et al.*, *PNAS* 86, 2365-2368 (1989)}. A molecular mechanism for the virus inducing activity is suggested by TNF α 's ability to activate a gene regulatory protein (NF κ B) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) {Osborn *et al.*, *PNAS* 86, 2336-2340 (1989)}. TNF α in AIDS associated cachexia is suggested by elevated serum TNF α and high levels of spontaneous TNF α production in peripheral blood monocytes from patients {Wright *et al.*, *J. Immunol.* 141(1), 99-104 (1988)}. TNF α has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

The nuclear factor κ B (NF κ B) is a pleiotropic transcriptional activator (Lenardo, *et al.*, *Cell* 1989, 58, 227-29). NF κ B has been implicated as a transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNF α and also to be an activator of HIV transcription (Dbaibo, *et al.*, *J Biol. Chem.* 1993, 17762-66; Duh *et al.*, *Proc. Natl. Acad. Sci.* 1989, 86, 5974-78; Bachelerie *et al.*, *Nature* 1991, 350, 709-12; Boswas *et al.*, *J Acquired*

Immune Deficiency Syndrome 1993, 6, 778-786; Suzuki *et al.*, *Biochem. And Biophys. Res. Comm.* 1993, 193, 277-83; Suzuki *et al.*, *Biochem. And Biophys. Res. Comm.* 1992, 189, 1709-15; Suzuki *et al.*, *Biochem. Mol. Bio. Int.* 1993, 31(4), 693-700; Shakhov *et al.*, *Proc. Natl. Acad. Sci. USA* 1990, 171, 35-47; and Staal *et al.*, *Proc.*
5 *Natl. Acad. Sci. USA* 1990, 87, 9943-47). Thus, inhibition of NF κ B binding can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful in the inhibition of a multitude of disease states. The compounds described herein can inhibit the action of NF κ B in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis,
10 rheumatoid spondylitis, osteoarthritis, other arthritic conditions, cancer, septic shock, sepsis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, inflammatory bowel disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS. TNF α and NF κ B levels are influenced by a reciprocal feedback loop. As noted above,
15 the compounds of the present invention affect the levels of both TNF α and NF κ B.

Many cellular functions are mediated by levels of adenosine 3',5'-cyclic monophosphate (cAMP). Such cellular functions can contribute to inflammatory conditions and diseases including asthma, inflammation, and other conditions (Lowe and Cheng, *Drugs of the Future*, 17(9), 799-807, 1992). It has been shown that the
20 elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators, including TNF α and NF κ B. Increased levels of cAMP also leads to the relaxation of airway smooth muscle.

The primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases

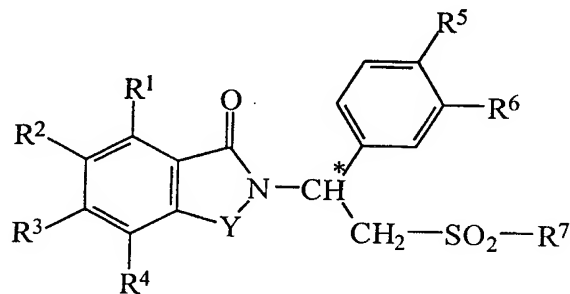
(PDE) (Beavo and Reitsnyder, *Trends in Pharm.*, **11**, 150-155, 1990). There are seven known members of the family of PDEs. It is recognized, for example, that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle (Verghese, et al., *Journal of Pharmacology and Experimental Therapeutics*, **272(3)**, 1313-1320, 1995). Thus, compounds that inhibit PDE IV specifically, would exhibit the desirable inhibition of inflammation and relaxation of airway smooth muscle with a minimum of unwanted side effects, such as cardiovascular or anti-platelet effects. Currently used PDE IV inhibitors lack the selective action at acceptable therapeutic doses. The compounds of the present invention are useful in the inhibition of phosphodiesterases, particularly PDE III and PDE IV, and in the treatment of disease states mediated thereby.

Decreasing $\text{TNF}\alpha$ levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases. These include but are not restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, radiation damage, and hyperoxic alveolar injury. Prior efforts directed to the suppression of the effects of $\text{TNF}\alpha$ have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies {Beutler *et al.*, *Science* 234, 470-474 (1985); WO 92/11383}.

Detailed Description

The present invention is based on the discovery that certain classes of non-polypeptide compounds more fully described herein decrease the levels of $\text{TNF}\alpha$.

In particular, the invention pertains to phenethylsulfone compounds of Formula I:



I

in which

the carbon atom designated * constitutes a center of chirality;

Y is $\text{C}=\text{O}$, CH_2 , SO_2 , or $\text{CH}_2\text{C}=\text{O}$;

each of R^1 , R^2 , R^3 , and R^4 , independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, or $-\text{NR}^8\text{R}^9$; or any two of R^1 , R^2 , R^3 , and R^4 on adjacent carbon atoms, together with the depicted phenylene ring are naphthylidene;

each of R^5 and R^6 , independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

R^7 is hydroxy, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, or NR^8R^9 ;

each of R^8 and R^9 taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of R^8 and R^9 is hydrogen and the other is $-\text{COR}^{10}$ or $-\text{SO}_2\text{R}^{10}$, or R^8 and R^9 taken together are tetramethylene,

pentamethylene, hexamethylene, or $-\text{CH}_2\text{CH}_2\text{X}^1\text{CH}_2\text{CH}_2-$ in which X^1 is $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$; and

each of $\text{R}^{8'}$ and $\text{R}^{9'}$ taken independently of the other is hydrogen, alkyl of 1 to 8 carbon atoms, phenyl, or benzyl, or one of $\text{R}^{8'}$ and $\text{R}^{9'}$ is hydrogen and the other is $-\text{COR}^{10'}$ or $-\text{SO}_2\text{R}^{10'}$, or $\text{R}^{8'}$ and $\text{R}^{9'}$ taken together are tetramethylene, pentamethylene, hexamethylene, or $-\text{CH}_2\text{CH}_2\text{X}^2\text{CH}_2\text{CH}_2-$ in which X^2 is $-\text{O}-$, $-\text{S}-$, or $-\text{NH}-$.

The term alkyl denotes a univalent saturated branched or straight hydrocarbon chain containing from 1 to 8 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and *tert.*-butyl. Alkoxy refers to an alkyl group bound to the remainder of the molecule through an ethereal oxygen atom. Representative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, and *tert.*-butoxy.

The term cycloalkyl as used herein denotes a univalent cyclic hydrocarbon chain which may be saturated or unsaturated. Unless otherwise stated, such chains can contain up to 18 carbon atoms and include monocycloalkyl, polycycloalkyl, and benzocycloalkyl structures. Monocycloalkyl refers to groups having a single ring group. Polycycloalkyl denotes hydrocarbon systems containing two or more ring systems with one or more ring carbon atoms in common; *i.e.*, a spiro, fused, or bridged structure. Benzocycloalkyl signifies a monocyclic alkyl group fused to a benzo group. Representative of monocycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, cyclotridecyl, cyclotetradecyl, cyclopentadecyl, cyclohexadecyl, cycloheptadecyl, and cyclooctadecyl. Representative of polycycloalkyl include decahydronaphthalene, spiro[4.5]decyl, bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, pinanyl, norbornyl, and bicyclo[2.2.2]octyl.

Benzocycloalkyl is typified by tetrahydronaphthyl, indanyl, and 1.2-benzocycloheptanyl. Cycloalkoxy refers to a cycloalkyl group as just described, that is a monocycloalkyl, polycycloalkyl, or benzocycloalkyl structure, bound to the remainder of the molecule through an ethereal oxygen atom.

- 5 It will be appreciated that by the term "sulfone" is used in a generic sense to included not only compounds of Formula I in which R^7 is alkyl, phenyl, benzyl, but also the corresponding sulfonic acids when R^7 is hydroxy, and sulfonamides when R^7 is NR^8R^9 .

A first preferred group of compounds are those of Formula I in which Y is $C=O$.

- 10 A further preferred group of compounds are those of Formula I in which Y is CH_2 .

A further preferred group of compounds are those of Formula I in which each of R^1 , R^2 , R^3 , and R^4 independently of the others, is hydrogen, halo, methyl, ethyl, methoxy, ethoxy, nitro, cyano, hydroxy, or $-NR^8R^9$ in which each of R^8 and R^9 taken independently of the other is hydrogen or methyl. or one of R^8 and R^9 is hydrogen and

- 15 the other is $-COCH_3$.

A further preferred group of compounds are those of Formula I in which one of R^1 , R^2 , R^3 and R^4 is $-NH_2$ and the remaining of R^1 , R^2 , R^3 and R^4 are hydrogen.

- 20 A further preferred group of compounds are those of Formula I in which one of R^1 , R^2 , R^3 , and R^4 is $-NHCOCH_3$ and the remaining of R^1 , R^2 , R^3 and R^4 are hydrogen.

A further preferred group of compounds are those of Formula I in which one of R^1 , R^2 , R^3 , and R^4 is $-N(CH_3)_2$ and the remaining of R^1 , R^2 , R^3 and R^4 are hydrogen.

A further preferred group of compounds are those of Formula I in which one of R^1 , R^2 , R^3 , and R^4 is methyl and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

A further preferred group of compounds are those of Formula I in which one of R^1 , R^2 , R^3 , and R^4 is fluoro and the remaining of R^1 , R^2 , R^3 , and R^4 are hydrogen.

- 5 A further preferred group of compounds are those of Formula I in which each of R^5 and R^6 , independently of the other, is hydrogen, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, cyclopentoxy, or cyclohexoxy.

A further preferred group of compounds are those of Formula I in which R^5 is methoxy and R^6 is monocycloalkoxy, polycycloalkoxy, and benzocycloalkoxy.

- 10 A further preferred group of compounds are those of Formula I in which R^5 is methoxy and R^6 is ethoxy.

A further preferred group of compounds are those of Formula I in which R^7 is hydroxy, methyl, ethyl, phenyl, benzyl, or $NR^{8'}R^{9'}$ in which each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen or methyl.

- 15 A further preferred group of compounds are those of Formula I in which R^7 is methyl, ethyl, phenyl, benzyl or $NR^{8'}R^{9'}$ in which each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen or methyl.

A further preferred group of compounds are those of Formula I in which R^7 is methyl.

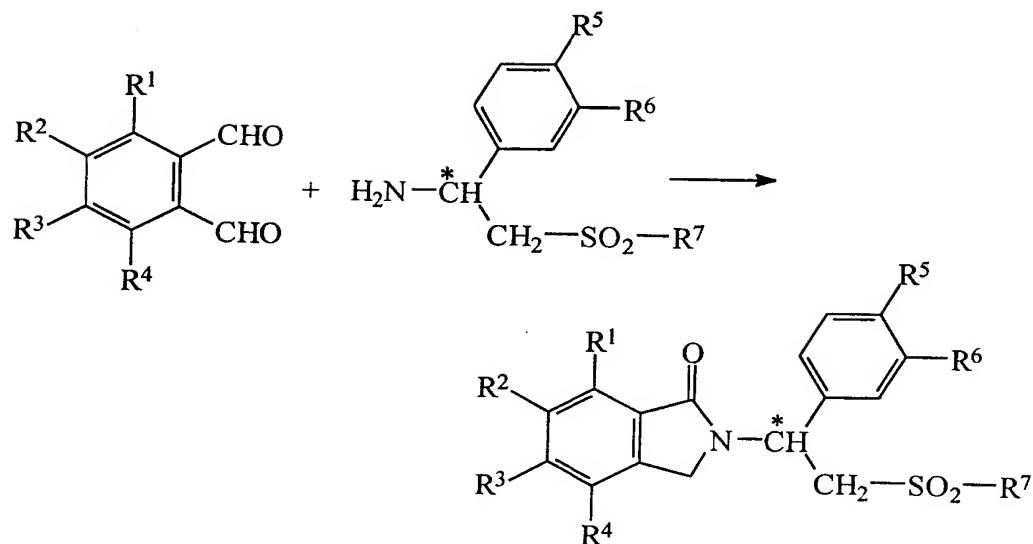
- 20 A further preferred group of compounds are those of Formula I in which R^7 is $NR^{8'}R^{9'}$ in which each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen or methyl.

The compounds of Formula I are used, under the supervision of qualified professionals, to inhibit the undesirable effects of $\text{TNF}\alpha$ and PDE IV. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment.

The compounds also can be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive $\text{TNF}\alpha$ and PDE IV production, respectively, such as viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, psoriasis, atopic dermatitis, etc.

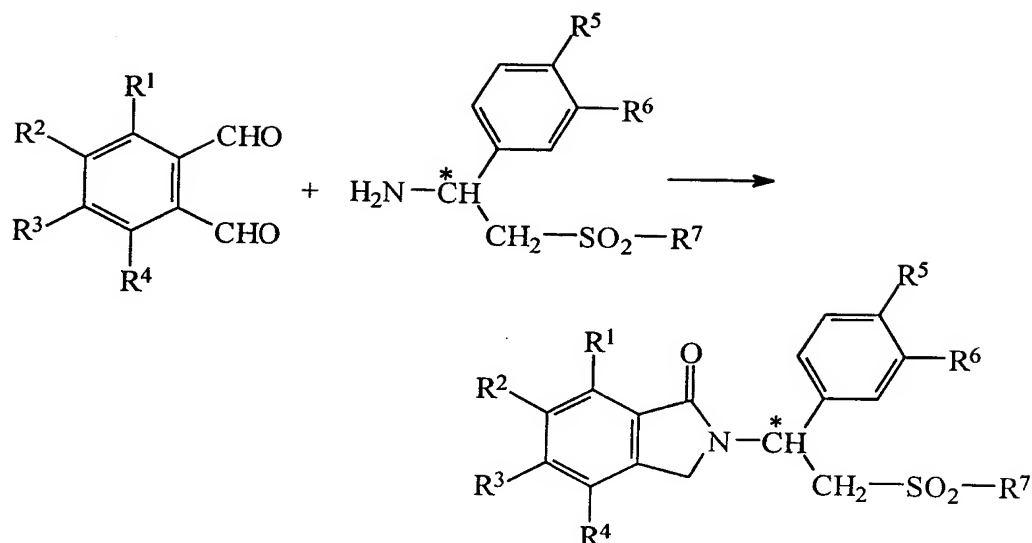
The compounds also can be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of $\text{TNF}\alpha$ production. $\text{TNF}\alpha$ mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

In a first embodiment, the isoindolinone compounds of the present invention in which Y is $\text{C}=\text{O}$ can be prepared through reaction of an appropriately substituted phthalic anhydride and a substituted ethylamine:



The two reagents are simply heated together, with or without a solvent, and the product isolated and purified by conventional means such as chromatography. When one of R^1 , R^2 , R^3 , and R^4 is to be amino in the final sulfone, it often is desirable to utilize the corresponding nitro compound in the reaction of the phthalic anhydride and substituted ethylamine and then catalytically convert the resulting nitroisoindolinone after formation. Alternatively, amino groups and other groups which may react can be converted to an appropriately protected group.

In a further embodiment, the isoindolinone compounds of the present invention in which Y is CH_2 can be prepared through reaction of an appropriately substituted phthalic dicarboxaldehyde and a substituted ethylamine:



Again the reagents need only be heated together, with or without a solvent, and the product isolated and purified by conventional means such as chromatography. As in the case of the phthalic anhydride used in the first embodiment, if one of R^1, R^2, R^3 and R^4 is to be amino in the final sulfone, the corresponding nitro compound is used and the resulting nitroisoindolinone then catalytically reduced. Alternatively, one can employ an appropriately protected group, both for amino groups and for any other groups which may react.

Protecting groups utilized herein denote groups which generally are not found in the final therapeutic compounds but which are intentionally introduced at some stage of the synthesis in order to protect groups which otherwise might be altered in the course of chemical manipulations. Such protecting groups are removed at a later stage of the synthesis and compounds bearing such protecting groups thus are of importance

primarily as chemical intermediates (although some derivatives also exhibit biological activity). Accordingly the precise structure of the protecting group is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example, "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973; Greene, Th. W. "Protective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides", Vol. 1, Schröder and Lubke, Academic Press, London and New York, 1965; "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol. 15/1, Georg Thieme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference.

10 An amino group can be protected as an amide utilizing an acyl group which is selectively removable under mild conditions, especially benzyloxycarbonyl, formyl, or a lower alkanoyl group which is branched in 1- or α -position to the carbonyl group, particularly tertiary alkanoyl such as pivaloyl, a lower alkanoyl group which is substituted in the position α to the carbonyl group, as for example trifluoroacetyl.

15 Coupling agents include such reagents as dicyclohexylcarbodiimide and N,N'-carbonyldiimidazole.

The compounds of Formula I possess a center of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbant. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, α -bromocamphoric acid,

methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; *i.e.*, in a form having an optical purity of >95%.

5 The present invention also pertains to the physiologically acceptable non-toxic acid addition salts of the compounds of Formula I. Such salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid,
10 salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like.

Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial
15 routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Pharmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed
20 with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories,

sterile injectable solutions and sterile packaged powders. Examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating
5 agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose
10 to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. The compositions can be formulated so as to provide an immediate, sustained or delayed release of active ingredient after administration to the patient by
15 employing procedures well known in the art.

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

Example 1

20 *1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine*

To a stirred solution of dimethyl sulfone (3.70 g, 39.4 mmol) in tetrahydrofuran (350 mL), was added n-butyllithium (17.5 mL, 2.5 M, 43.8 mmol) under nitrogen at -78° C and the mixture was stirred at 78° C for 25 min. To a stirred solution of 3-ethoxy-4-methoxybenzaldehyde (7.10 g, 39.4 mmol) in tetrahydrofuran (40 mL) under nitrogen
25 in a separate flask at 0° C was added lithium hexamethyldisilazide (43.0 mL, 1.0 M,

43.0 mmol) in hexane. After 15 min, boron trifluoride etherate (10.0 mL, 78.9 mmol) was added to the resulting mixture at 0° C. After 5 min, this solution was added to the -78° C sulfone solution via syringe. The solution was allowed to warm to room temperature over one hour. The resulting mixture was then quenched with potassium carbonate (32 g) and water (200 mL). The mixture was stirred for 30 min and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 X 200 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), and then dried over magnesium sulfate. The solvent was removed *in vacuo* and the resulting solid stirred with ether (100 mL) and 4 N hydrochloric acid (100 mL) for 15 min. The aqueous layer was separated and the organic layer extracted with 4 N hydrochloric acid (30 mL). The combined aqueous layers were washed with ether (50 mL), stirred, and cooled in an ice bath and the pH adjusted to 14 with sodium hydroxide (5 N). This solution was extracted with ethyl acetate (3 X 100 mL) and the combined organic layers were washed with brine (50 mL) and dried over sodium carbonate and sodium sulfate. Removal of solvent *in vacuo* gave an oil which was stirred with ether (20 mL) for 20 min to give a suspension. The suspension was filtered and the solid was washed with ether (20 mL) and then dried in a vacuum oven to yield 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl ethylamine as an off-white solid (4.17 g, 39%): mp, 116.5-117.0° C; ¹H NMR (CDCl₃) δ 1.47 (t, *J* = 7 Hz, 3H, CH₃), 1.92 (br s 2H, NH₂), 2.91 (s, 3H, SO₂CH₃), 3.19 (dd, *J* = 3.5, 14 Hz, 1H, CHH), 3.36 (dd, *J* = 9.3, 14 Hz 1H, CHH), 3.87 (s, 3H, CH₃), 4.10 (q, *J* = 7 Hz, 2H, CH₂), 4.60 (dd, *J* = 3.5, 9 Hz, 1H, CH), 6.83-6.93 (m, 3H, Ar); ¹³C NMR (CDCl₃) δ 14.75, 42.42, 50.94, 55.99, 63.18, 64.44, 110.71, 111.67, 118.21, 135.55, 148.72, 149.09; Anal Calcd for C₁₂H₁₉NO₄S: C, 52.73; H, 7.01; N, 5.12. Found: C, 52.82; H, 6.69; N, 4.99.

Example 2***1-(3-Ethoxy-4-methoxyphenyl)-2-(N,N-dimethylaminosulfonyl)ethylamine***

1-(3-Ethoxy-4-methoxyphenyl)-2-(N,N-dimethylaminosulfonyl)ethylamine was prepared by a procedure analogous to that of Example 1 from N,N-dimethyl methanesulfonamide (685 mg, 5.56 mmol) and n-butyllithium (2.5 mL, 2.5 M, 6.3 mmol) in tetrahydrofuran (90 mL), and 3-ethoxy-4-methoxybenzaldehyde (1.0 g, 5.5 mmol), lithium hexamethyldisilazide (4.7 mL, 1.3 M, 6.1 mmol) and boron trifluoride etherate (1.4 mL, 11 mmol) in tetrahydrofuran (5 mL). The product was obtained as a white solid (360 mg, 21% yield): mp, 82.0-83.0° C; ¹H NMR (CDCl₃); δ 1.48 (t, *J* = 7.5 Hz, 3H, CH₃), 1.91 (br s, 2H, NH₂), 2.88 (s, 6H, N(CH₃)₂), 3.05 (dd, *J* = 3.0, 13.5 Hz, 1H, CHH), 3.12 (dd, *J* = 9.2, 13.5 Hz, 1H, CHH), 3.88 (s, 3H, CH₃), 4.12 (q, *J* = 7.0 Hz, 2H, CH₂), 4.61 (dd, *J* = 2.9, 9.2 Hz, 1H, NCH), 6.83-6.99 (m, 3H, Ar); ¹³C NMR (CDCl₃) δ 14.81, 37.42, 51.02, 56.03, 64.41, 110.74, 111.55, 118.35, 135.97, 148.64, 148.96; Anal Calcd for C₁₃H₂₂NO₄S: C, 51.64; H, 7.33; N, 9.26. Found: C, 51, 41; H, 7.11; N, 9.10.

Example 3***2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindolin-1-one***

A stirred mixture 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (100 mg, 0.37 mmol) and 1,2-phthalic dicarboxaldehyde (49 mg, 0.37 mmol) in acetic acid (2 mL) was heated to reflux for 15 min. Removal of solvent *in vacuo* and chromatography gave an oil which was stirred with ether (2 mL). The resulting suspension was filtered to yield 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindolin-1-one as a light yellow solid (100 mg, 70% yield): mp, 130.0-134.0° C; ¹H NMR (CDCl₃) δ 1.45 (t, *J* = 7 Hz, 3H, CH₃), 2.96 (s, 3H, CH₃), 3.70 (dd, *J* = 4.5, 14.7 Hz, 1H, CHH), 3.86 (s, 3H, CH₃), 4.07 (q, *J* = 6.9 Hz, 2H, CH₂), 4.25 (d, *J* = 16.5 Hz, 1 H, CHH), 4.31 (dd, *J* = 10.3, 14.5 Hz, 1H, CHH), 4.46 (d, *J* = 16

HZ, 1H, CHH), 5.71 (dd, $J = 4.5, 10.3$ Hz, 1H, NCH), 6.84-7.01 (m, 3H, Ar), 7.38-7.56 (m, 3H, Ar), 7.85 (d, $J = 6.9$ Hz, 1H, Ar); ^{13}C NMR (CDCl_3) δ 14.65, 41.33, 46.27, 52.33, 55.95, 56.00, 65.56, 111.45, 112.28, 119.30, 122.85, 123.85, 128.13, 129.89, 131.80, 132.27, 141.26, 148.88, 149.62, 169.09; Anal Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_5\text{S}$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.68, H, 6.06; N, 3.62.

Example 4

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(N,N-dimethylaminosulfonyl)ethyl]isoindolin-1-one

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-(N,N-dimethylaminosulfonyl)ethyl]isoindolin-1-one was prepared by the procedure of Example 3 from 1-(3-ethoxy-4-methoxyphenyl)-2-(N,N-dimethylaminosulfonyl)ethylamine (150 mg, 0.49 mmol) and 1,2-phthalic dicarboxaldehyde (67 mg, 0.49 mmol) in acetic acid (2 mL). The product was obtained as a solid (142 mg, 69% yield): mp, 165.0-167.0° C; ^1H NMR (CDCl_3) δ 1.45 (t, $J = 7$ Hz, 3H, CH_3), 2.86 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.58 (dd, $J = 4.7, 14.4$ Hz, 1H, CHH), 3.86 (s, 3H, CH_3), 4.08 (q, $J = 7$ Hz, 2H, CH_2), 4.30 (d, $J = 16.5$ Hz, 1H, NCHH), 4.33 (dd, $J = 9, 14.4$ Hz, 1H, CHH), 4.49 (d, $J = 16.5$ Hz, 1H, NCHH), 5.60 (dd, $J = 4.7, 9.5$ Hz, 1H, NCH), 6.83 (d, $J = 8.3$ Hz, 1H, Ar), 6.98 (dd, $J = 2, 8.3$ Hz, 1H, Ar), 7.06 (d, $J = 2$ Hz, 1H, Ar), 7.37-7.56 (m, 3H, Ar), 7.84 (d, $J = 7$ Hz, 1H, Ar), ^{13}C NMR (CDCl_3) δ 14.69, 37.31, 48.64, 49.73, 52.91, 52.95, 64.54, 111.31, 112.46, 119.29, 122.76, 123.72, 128.03, 130.67, 131.55, 132.75, 141.26, 148.73, 149.39, 168.63; Anal Calcd for $\text{C}_{21}\text{H}_{26}\text{NO}_5\text{S}$: C, 60.27; H, 6.26; N, 6.69. Found: C, 60.04; H, 6.10; N, 6.62.

Example 5

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonyl]ethyl]isoindoline-1,3-dione

A mixture of 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (200 mg, 0.73 mmol) and sodium hydrogen carbonate (80 mg, 0.95 mmol) in acetonitrile and water (2 mL each) was stirred under nitrogen at room temperature for 2 minutes. To the resulting solution was added N-ethoxycarbonylphthalimide (170 mg, 0.78 mmol).
5 After 17 hours, the resulting solution was stirred with hydrochloric acid (2 mL, 4 N), and water (30 mL) at room temperature for 30 minutes. The resulting suspension was filtered and the solid was washed with water (2 X 25 mL), and then dried in a vacuum oven overnight (60° C, < 1 torr) to yield 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]isoindoline-1,3-dione as a solid (206 mg, 70% yield): mp, 151.0-
10 152.0° C; ¹H NMR (CDCl₃); δ 1.46 (t, *J* = 6.9 Hz, 3H, CH₃), 2.84 (s, 3H, CH₃), 3.78 (dd, *J* = 4.8, 14.4 Hz, 1H, CHH), 3.84 (s, 3H, CH₃), 4.10 (q, *J* = 7 Hz, 2H, CH₂), 4.54 (dd, *J* = 10.1, 14.4 Hz, 1H, CHH), 5.90 (dd, *J* = 4.8, 10.1 Hz, 1H, NCH), 6.83 (d, *J* = 8.5 Hz, 1H, Ar), 7.11-7.15 (m, 2H, Ar), 7.67-7.73 (m, 2H, Ar), 7.80-7.84 (m, 2H, Ar); ¹³C NMR (CDCl₃) δ 14.63, 41.49, 48.84, 54.82, 55.89, 64.45, 111.43, 112.50, 120.43,
15 123.51, 129.56, 131.58, 134.17, 148.57, 149.63, 167.80; Anal Calcd for C₂₀H₂₁NO₆S: C, 59.54; H, 5.25; N, 3.47. Found: C, 59.66; H, 5.28; N, 3.29.

Example 6

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-nitro-isoindoline-1,3-dione

20 A stirred mixture of 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (1.0 g, 3.7 mmol) and 4-nitrophthalic anhydride (706 mg, 3.66 mmol) was heated to melt for 6 min. The mixture was allowed to cool to room temperature. Chromatography of the resulting oil gave 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-nitro-isoindoline-1,3-dione as a solid (1.42 g, 87% yield): mp,
25 255.0-256.0° C; ¹H NMR (CDCl₃); δ 1.47 (t, *J* = 7 Hz, 3H, CH₃), 2.91 (s, 3H, CH₃), 3.71 (dd, *J* = 4.2, 14.3 Hz, 1H, CHH), 3.85 (s, 3H, CH₃), 4.10 (q, *J* = 7 Hz, 2H, CH₂),

4.59 (dd, $J = 11.1, 14.1$, Hz, 1H, CHH), 5.94 (dd, $J = 4.1, 10.9$ Hz, 1H, NCH), 6.82-6.86 (m, 2H, Ar), 7.09-7.14 (m, 2H, Ar), 8.01-8.04 (m, 1H, Ar), 8.56-8.65 (m, 1H, Ar), ^{13}C NMR (CDCl_3) δ 14.67, 41.61, 49.16, 53.99, 55.96, 64.54, 111.48, 112.39, 118.98, 120.48, 124.79, 128.73, 129.39, 133.06, 136.03, 148.71, 149.92, 151.79, 165.56, 165.74; Anal Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_8\text{S}$: C, 53.57; H, 4.50; N, 6.23. Found: C, 53.59; H, 4.58; N, 5.88.

Example 7

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-aminoisoindoline-1,3-dione

A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-nitro-isoindoline-1,3-dione (600 mg, 1.33 mmol) and Pd/C (100 mg, 10%) in ethyl acetate (40 mL) was shaken under hydrogen (50 psi) for 7 h in Parr type shaker. The mixture was filtered through a pad of celite, and the pad was washed with ethyl acetate (50 mL). The filtrate was concentrated *in vacuo* to give a solid. The solid was stirred in a mixture of methylene chloride (2 mL) and hexane (10 mL). The resulting suspension was filtered to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-aminoisoindoline-1,3-dione as a yellow solid (500 mg, 90% yield): mp, 224.5-227.0°C; ^1H NMR ($\text{DMSO}-d_6$) δ 1.32 (t, $J = 6.8$ Hz, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.00 (q, $J = 7$ Hz, 2H, CH_2), 4.03-4.09 (m, 1H, CHH), 4.34 (dd, $J = 10.3, 14.2$ Hz, 1H, CHH), 5.70 (dd, $J = 3.7, 10.2$ Hz, 1H, NCH), 6.52 (br s, 2H, NH_2), 6.79-6.81 (m, 1H, Ar), 6.92 (br s, 3H, Ar), 7.06 (br s, 1H, Ar), 7.48 (d, $J = 8.2$ Hz, 1H, Ar); ^{13}C NMR ($\text{DMSO}-d_6$) δ 14.64, 40.99, 46.99, 53.34, 55.46, 63.80, 106.99, 111.78, 112.31, 116.12, 116.80, 118.61, 125.12, 130.33, 134.11, 147.80, 148.74, 155.13, 167.39, 167.86; Anal Calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_6\text{S}$: 57.41; H, 5.30; N, 6.69. Found: C, 57.03; H, 5.40; N, 6.33.

Example 8***2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-nitroisoindoline-1,3-dione***

A stirred solution 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (640
5 mg, 2.34 mmol) and 3-nitrophthalic anhydride (460 mg, 2.34 mmol) in acetic acid (10
mL) was heated at reflux for 15 h. The solvent was removed *in vacuo* to yield an oil.
Chromatography of the resulting oil yielded 2-[1-(3-ethoxy-4-methoxyphenyl)-2-
methylsulfonylethyl]-4-nitroisoindoline-1,3-dione as a yellow solid (850 mg, 81%
yield): mp, 110.0-114.0° C; ¹H NMR (CDCl₃); δ 1.47 (t, *J* = 7.0 Hz, 3H, CH₃), 2.90 (s,
10 3H, CH₃), 3.71 (dd, *J* = 4.3, 14.4 Hz, 1H, CHH), 3.85 (s, 3H, CH₃), 4.10 (q, *J* = 7.0 Hz,
2H, CH₂), 4.58 (dd, *J* = 10.7, 14.4 Hz, 1H, CHH), 5.93 (dd, *J* = 4.2, 10.7 Hz, 1H,
NCH), 6.84 (d, *J* = 8.8 Hz, 1H, Ar), 7.11-7.15 (m, 2H, Ar), 7.89 (t, *J* = 7.8 Hz, 1H, Ar),
8.08-8.13 (m, 2H, Ar); ¹³C NMR (CDCl₃) δ 14.67, 41.56, 49.19, 53.97, 55.96, 64.56,
111.52, 112.51, 120.62, 123.44, 127.35, 128.65, 128.84, 133.73, 135.48, 145.24,
15 148.68, 149.92, 162.53, 165.33; Anal Calcd for C₂₀H₂₀NO₈S: C, 53.57; H, 4.50; N,
6.23. Found: C, 53.54; H, 4.28; N, 6.32

Example 9***2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione***

20 A mixture of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-nitroiso-
indoline-1,3-dione (710 mg, 1.58 mmol) and Pd/C (200 mg) in ethyl acetate/acetone
(40 mL each) was shaken under H₂ (50 psi) in a Parr Type Shaker for 5 hours. The
suspension was filtered through a pad of magnesium sulfate. The filtrate was
concentrated *in vacuo* to give an oil. The oil was stirred with ethyl acetate (a mL),
25 hexane (2 mL) and ether (2ML) for 1 h. The resulting suspension was filtered and the
solid was dried in a vacuum oven to give 2-[1-(3-ethoxy-4-methoxyphenyl)-2-
methylsulfonylethyl]-4-aminoisoindoline-1,3-dione as a yellow solid (550 mg, 83%

yield): mp, 135.0-137.5° C; ¹H NMR (DMSO-d₆) δ 1.32 (t, *J* = 6.9 Hz, 3H, CH₃), 3.00 (s, 3H, CH₃), 3.73 (s, 3H, CH₃), 4.00 (q, *J* = 6.9 Hz, 2H, CH₂), 4.08 (dd, *J* = 4.2, 14.5 Hz, 1H, CHH), 4.36 (dd, *J* = 10.8, 14.2 Hz, 1H, CHH), 5.72 (dd, *J* = 4.1, 10.3 Hz, 1H, NCH), 6.51 (br s, SH, NH₂), 6.89-7.07 (m, 5H, Ar), 7.43 (t, *J* = 7.4, Hz, 1H, Ar); ¹³C NMR (CDCl₃) δ 14.68, 41.55, 48.62, 55.23, 55.93, 64.48, 110.70, 111.42, 112.52, 112.96, 120.38, 121.30, 129.95, 132.23, 135.37, 145.56, 148.56, 149.56, 168.19, 169.43; Anal Calcd for C₂₀H₂₂NO₆S: C, 57.41; H, 5.30; N, 6.69. Found C, 57.11; H, 5.23; N, 6.43.

Example 10

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-methyl-isoindoline-1,3-dione

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-methylisoindoline-1,3-dione was prepared by the procedure of Example 8 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethylamine (1.4 g, 5.0 mmol) and 3-methylphthalic anhydride (810 mg, 5.0 mmol) in acetic acid (15 mL) to afford 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethylamine (1.0 g, 3.7 mmol) and 3-methylphthalic anhydride (590 mg, 3.7 mmol). The product was obtained as a white solid (1.78 g, 85% yield); mp, 143.0-145.0° C; ¹H NMR (CDCl₃) δ 1.46 (t, *J* = 7.0 Hz, 3H, CH₃), 2.67 (s, 3H, CH₃), 2.83 (s, 3H, CH₃), 3.79 (dd, *J* = 4.8, 14.5 Hz, 1H, CHH), 3.85 (s, CH, CH₃), 4.11 (q, *J* = 7.0 Hz, 2H, CH₂), 4.54 (dd, *J* = 9.8, 14.5 Hz, 1H, CHH), 5.89 (dd, *J* = 4.8, 9.9 Hz, 1H, NCH), 6.81-6.85 (m, 1H, Ar), 7.65 (d, *J* = 7.5 Hz, 1H, Ar); ¹³C NMR (CDCl₃) δ 14.65, 17.54, 41.49, 48.63, 54.89, 55.89, 64.44, 111.36, 112.48, 120.44, 121.17, 128.24, 129.69, 132.00, 133.69, 136.63, 138.29, 148.51, 149.55, 167.99, 168.46; Anal Calcd for C₂₁H₂₃NO₆S: C, 60.42; H, 5.55; N, 3.36. Found: C, 60.68; H, 5.40; N, 3.15.

Example 11***2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-methyl-isoindoline-1,3-dione***

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-methylisoindoline-1,3-dione was prepared by the procedure of Example 6 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (1.0 g, 3.7 mmol) and 4-methylphthalic anhydride (590 mg, 3.7 mmol). The product was obtained as a white solid (710 mg, 46% yield): mp, 87.0-89.0° C; ¹H NMR (CDCl₃) δ 1.45 (t, *J* = 7.0 Hz, 3H, CH₃), 2.47 (s, 3H, CH₃), 2.84 (s, 3H, CH₃), 3.77-3.84 (m, 1H, CHH), 3.84 (s, 3H, CH₃), 4.09 (q, *J* = 7.0 Hz, 2H, CH₂), 4.54 (dd, *J* = 10.2, 14.4 Hz, 1H, CHH), 5.89 (dd, *J* = 4.7, 10.1 Hz, 1H, NCH), 6.83 (d, *J* = 8.0 Hz, 1H, Ar), 7.09-7.15 (m, 2H, Ar), 7.47 (d, *J* = 7.7 Hz, 1H, Ar), 7.60 (s, 1H, Ar), 7.67 (d, *J* = 7.6 Hz, 1H, Ar); ¹³C NMR (CDCl₃) δ 14.51, 21.77, 41.31, 48.56, 54.59, 55.73, 64.26, 111.24, 112.31, 120.25, 123.26, 123.86, 128.81, 129.57, 131.79, 134.59, 145.43, 148.34, 149.36, 167.72, 167.87; Anal Calcd for C₂₁H₂₃NO₆S: C, 60.42; H, 5.55; N, 3.36. Found: C, 60.34; H, 5.49; N, 3.21.

Example 12***2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetamido-isoindoline-1,3-dione***

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetamidoisoindoline-1,3-dione was prepared by the procedure of Example 8 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (1.0 g, 3.7 mmol) and 3-acetamidophthalic anhydride (751 mg, 3.66 mmol) in acetic acid (20 mL). The product was obtained as a yellow solid (1.0 g, 59% yield): mp, 144.0° C; ¹H NMR (CDCl₃) δ 1.47 (t, *J* = 7.0 Hz, 3H, CH₃), 2.26 (s, 3H, CH₃), 2.88 (s, 3H, CH₃), 3.75 (dd, *J* = 4.4, 14.3 Hz, 1H, CHH), 5.87 (dd, *J* = 4.3, 10.5 Hz, 1H, NCH), 6.82-6.86 (m, 1H, Ar), 7.09-7.11 (m, 2H, Ar), 9.49 (br s, 1H, NH), ¹³C NMR (CDCl₃) δ 14.61, 24.85, 41.54, 48.44, 54.34, 55.85, 64.43, 111.37, 112.34, 115.04, 118.11, 120.21, 124.85, 129.17, 130.96,

136.01, 137.52, 148.54, 149.65, 167.38, 169.09, 169.40; Anal Calcd for $C_{22}H_{24}NO_7S$: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.31; H, 5.34; N, 5.83.

Example 13

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-acetamido-isoindoline-1,3-dione

5
2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-acetamidoisoindoline-1,3-dione was prepared by the procedure of Example 6 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (1.0 g, 3.7 mmol) and 4-acetamidophthalic anhydride (751 mg, 3.66 mmol). The product was obtained as a
10 yellow solid (330 mg, 20% yield): mp, 215.0-217.0° C; 1H NMR (DMSO- d_6) δ 1.32 (t, J = 6.9 Hz, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.00 (q, J = 7.0 Hz, 2H, CH_2), 4.12 (dd, J = 4.5, 14.3 Hz, 1H, CHH), 4.35 (dd, J = 10.5, 14.2 Hz, 1H, CHH), 5.76 (dd, J = 4.5, 10.5 Hz, 1H, NCH), 6.90-6.98 (m, 2H, Ar), 7.08 (br s, 1H, Ar), 7.83-7.84 (m, 2H, Ar), 8.19 (br s, 1H, Ar), 10.95 (br s, 1H, NH); ^{13}C NMR
15 (DMSO- d_6) δ 14.66, 24.22, 41.05, 47.35, 53.07, 55.47, 63.80, 111.74, 112.28, 112.72, 123.34, 124.59, 124.66, 129.74, 132.68, 145.00, 147.85, 148.84, 167.00, 167.28, 169.36; Anal Calcd for $C_{22}H_{24}NO_7S$: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.13; H, 5.18; N, 5.74.

Example 14

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-dimethylamino isoindoline-1,3-dione

20
2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-dimethylaminoisoindoline-1,3-dione was prepared by the procedure of Example 8 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (572 mg, 2.09 mmol) and 3-dimethylaminophthalic anhydride (400 mg, 2.09 mmol) in acetic acid (20 mL). The
25 product was obtained as a yellow solid (740 mg, 80% yield): mp, 94.0-96.0° C; 1H NMR (CDCl $_3$) δ 1.46 (t, J = 7.0 Hz, 3H, CH_3), 2.82 (s, 3H, CH_3), 3.08 (s, 6H, CH_3),

3.76-3.84 (m, 1H, CHH), 3.82 (s, 3H, CH₃), 4.11 (q, $J = 7.0$ Hz, 2H, CH₂), 4.54 (dd, $J = 9.9, 14.5$ Hz, 1H, CHH), 5.88 (dd, $J = 4.8, 9.9$ Hz, 1H, NCH), 6.81-6.84 (m, 1H, Ar), 7.04-7.15 (m, 3H, Ar), 7.23-7.27 (m, 1H, Ar), 7.48 (dd, $J = 7.3, 8.3$ Hz, 1H, Ar); ¹³C NMR (CDCl₃) δ 14.68, 41.47, 43.39, 48.74, 55.20, 55.92, 64.43, 111.34, 112.54, 113.78, 114.41, 120.47, 122.09, 129.97, 134.32, 134.81, 148.46, 149.44, 150.42, 167.06, 168.19; Anal Calcd for C₂₂H₂₆NO₆S: C, 59.14; H, 5.91; N, 6.27. Found: C, 59.14; H, 5.91; N, 6.10.

Example 15

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-dimethylamino-isoindoline-1,3-dione

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-

dimethylaminoisoindoline-1,3-dione was prepared by the procedure of Example 8 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (572 mg, 2.09 mmol) and 4-dimethylaminophthalic anhydride (400 mg, 2.09 mmol) in acetic acid (20 mL). The product was obtained as a yellow solid (200 mg, 21% yield): mp, 161.5-163.5° C; ¹H NMR (DMSO-d₆) δ 1.46 (t, $J = 6.9$ Hz, 3H, CH₃), 2.79 (s, 3H, CH₃), 3.09 (s, 6H, CH₃), 3.78-3.85 (m, 1H, CHH), 3.85 (s, 3H, CH₃), 4.11 (q, $J = 7.0$ Hz, 2H, CH₂), 4.51 (dd, $J = 9.7, 14.6$ Hz, 1H, NCHH), 5.85 (dd, $J = 5.1, 9.6$ Hz, 1H, NCH), 6.75-6.84 (m, 2H, Ar), 7.03 (d, $J = 2.3$ Hz, 1H, Ar), 7.10-7.16 (m, 2H, Ar), 7.61 (d, $J = 8.5$ Hz, 1H, Ar), ¹³C NMR (DMSO-d₆) δ 14.65, 40.40, 41.43, 48.83, 55.42, 55.89, 64.38, 105.80, 111.29, 112.43, 114.86, 116.90, 120.38, 125.11, 130.14, 134.27, 148.46, 149.38, 154.44, 168.14, 168.67; Anal Calcd for C₂₂H₂₆NO₆S + 0.2 H₂O: C, 58.70; H, 5.91; N, 6.22. Found: C, 58.70; H, 5.93; N, 5.84.

Example 16***2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]benzo[e]isoindoline-1,3-dione***

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]benzo[e]isoindoline-1,3-dione was prepared by the procedure of Example 8 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (1.31 g, 4.79 mmol) and 1,2-naphthalic anhydride (950 mg, 4.79 mmol) in acetic acid (15 mL). The product was obtained as a yellow solid (1.65 g, 76% yield): mp, 158.0-159.5° C; ¹H NMR (DMSO-d₆) δ 1.33 (t, *J* = 6.9 Hz, 3H, CH₃), 3.03 (s, 3H, CH₃), 3.73 (s, 3H, CH₃), 4.03 (q, *J* = 6.9 Hz, 2H, CH₂), 4.18 (dd, *J* = 4.3, 14.3 Hz, 1H, CHH), 4.41 (dd, *J* = 10.7, 14.4 Hz, 1H, CHH), 5.86 (dd, *J* = 4.2, 10.3 Hz, 1H, NCH), 6.83-6.96 (m, 1H, Ar), 7.03-7.07 (m, 1H, Ar), 7.15 (br s, 1H, Ar), 7.70-7.90 (m, 3H, Ar), 8.15 (d, *J* = 8.0 Hz, 1H, Ar), 8.39 (d, *J* = 8.3 Hz, 1H, Ar), 8.76 (d, *J* = 8.2 Hz, 1H, Ar); ¹³C NMR (DMSO-d₆) δ 19.86, 46.29, 52.48, 58.35, 60.67, 69.03, 116.96, 117.57, 123.65, 124.97, 128.97, 131.40, 132.30, 134.15, 134.36, 134.94, 135.16, 135.89, 140.85, 153.09, 154.06, 173.09, 173.82; Anal Calcd for C₂₄H₂₃NO₆S: C, 63.56; H, 5.11; N, 3.09. Found: C, 63.33; H, 5.06; N, 2.95.

Example 17***2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-methoxyisoindoline-1,3-dione***

2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-methoxyisoindoline-1,3-dione was prepared by the procedure of Example 8 from 1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethylamine (580 mg, 2.12 mmol) and 3-methoxyphthalic anhydride (380 mg, 2.13 mmol) in acetic acid (15 mL). The product was obtained as a white solid (620 mg, 67% yield): mp, 162.5-164.5° C; ¹H NMR (CDCl₃) δ 1.45 (t, *J* = 6.9 Hz, 3H, CH₃), 2.85 (s, 3H, CH₃), 3.78 (dd, *J* = 4.7, 10.5 Hz, 1H, CHH), 3.84 (s, 3H, CH₃), 3.99 (s, 3H, CH₃), 4.09 (q, *J* = 6.9 Hz, 2H, CH₂), 4.54 (dd, *J* = 10.3, 14.4 Hz, 1H, CHH), 5.87 (dd, *J* = 4.6, 10.7 Hz, 1H, NCH), 6.80-6.83 (m,

1H, Ar), 7.10-7.18 (m, 3H, Ar), 7.38 (d, $J = 7.3$ Hz, 1H, Ar), 7.63 (dd, $J = 7.5, 8.2$ Hz, 1H, Ar); ^{13}C NMR (CDCl_3) δ 14.57, 41.32, 48.52, 54.62, 55.82, 56.19, 64.38, 111.35, 112.52, 115.56, 116.75, 117.58, 120.40, 129.58, 133.59, 136.30, 148.41, 149.46, 156.74, 166.43, 167.35; Anal Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_7\text{S}$: C, 58.19; H, 5.35; N, 3.23.

5 Found: C, 58.05; H, 5.35; N, 3.24.

Example 18

Tablets, each containing 50 mg of 1-oxo-2-(2,6-dioxo-3-methylpiperidin-3-yl)-4,5,6,7 tetrafluoroisindoline, can be prepared in the following manner:

Constituents (for 1000 tablets)

10	2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methylsulfonyl-ethyl]isoindolin-1-one.....	50.0 g
	lactose.....	50.7 g
	wheat starch.....	7.5 g
15	polyethylene glycol 6000	5.0 g
	talc.....	5.0 g
	magnesium stearate	1.8 g
	demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The
 20 active ingredient, lactose, talc, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 mL of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C, forced
 25 through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 19

Tablets, each containing 100 mg of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(N,N-dimethylaminosulfonyl)ethyl]isoindolin-1-one, can be prepared in the following manner:

5	<u>Constituents</u> (for 1000 tablets)
	2-[1-(3-ethoxy-4-methoxy- phenyl)-2-(N,N-dimethyl- aminosulfonyl)ethyl]- isoindolin-1-one 100.0 g
10	lactose..... 100.0 g
	wheat starch..... 47.0 g
	magnesium stearate 3.0 g

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to 100 mL of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 20

Tablets for chewing, each containing 75 mg of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl]isoindoline-1,3-dione, can be prepared in the following manner:

	<u>Composition</u> (for 1000 tablets)
25	2-[1-(3-ethoxy-4-methoxy- phenyl)-2-methylsulfonyl- ethyl]isoindoline-1,3-dione 75.0 g
	mannitol 230.0 g
	lactose..... 150.0 g
30	talco 21.0 g
	glycine 12.5 g
	stearic acid..... 10.0 g
	saccharin..... 1.5 g
	5% gelatin solution..... q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50° C and again forced through a sieve of 1.7 mm mesh width. 2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]isoindoline-1,3-dione, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

Example 21

Tablets, each containing 10 mg of 2-(2,6-dioxoethylpiperidin-3-yl)-4-aminophthalimide, can be prepared in the following manner:

Composition (for 1000 tablets)

2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methylsulfonyl-ethyl]-5-nitro-isoindoline-1,3-dione.....	10.0 g
lactose.....	328.5 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talc	25.0 g
magnesium stearate	4.0 g
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of

approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 22

Gelatin dry-filled capsules, each containing 100 mg of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-aminoisoindoline-1,3-dione, can be prepared in the following manner:

	<u>Composition</u> (for 1000 capsules)
	2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methylsulfonyl-ethyl]-4-aminoisoindoline-1,3-dione..... 100.0 g
10	microcrystalline cellulose..... 30.0 g
	sodium lauryl sulfate..... 2.0 g
	magnesium stearate..... 8.0g

15 The sodium lauryl sulfate is sieved into the 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-aminoisoindoline-1,3-dione through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is
20 added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

Example 23

25 A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

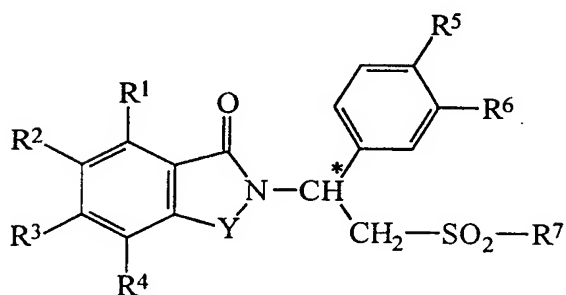
	2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methylsulfonyl-ethyl]-4-aminoisoindoline-1,3-dione hydrochloride	5.0 g
30	sodium chloride.....	22.5 g
	phosphate buffer pH 7.4..	300.0 g
	demineralized water .. to	2500.0 mL
	2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-aminoisoindoline-1,3-	

dioxoisoindoline as the hydrochloride is dissolved in 1000 mL of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 mL with water. To prepare dosage unit forms, portions of 1.0 or 2.5 mL each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of active
5 ingredient).

Claims

1. A sulfone selected from the group consisting of

(a) a compound of the formula:



in which:

the carbon atom designated * constitutes a center of chirality;

Y is C=O, CH₂, SO₂ or CH₂C=O;

each of R¹, R², R³, and R⁴, independently of the others, is hydrogen, halo, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, nitro, cyano, hydroxy, or -NR⁸R⁹; or any two of R¹, R², R³, and R⁴ on adjacent carbon atoms, together with the depicted phenylene ring are naphthylidene

each of R⁵ and R⁶, independently of the other, is hydrogen, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cyano, or cycloalkoxy of up to 18 carbon atoms;

R⁷ is hydroxy, alkyl of 1 to 8 carbon atoms, phenyl, benzyl, or NR⁸R⁹;

1 each of R^8 and R^9 taken independently of the other is hydrogen, alkyl of 1 to 8
2 carbon atoms, phenyl, or benzyl, or one of R^8 and R^9 is hydrogen and the
3 other is $-\text{COR}^{10}$, $-\text{SO}_2\text{R}^{10}$, or $-\text{NH COR}^{10}$, or R^8 and R^9 taken together are
4 tetramethylene, pentamethylene, hexamethylene, or $-\text{H}_2\text{CH}_2\text{X}^1\text{CH}_2-$ in
5 which X^1 is $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$;

6 each of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen, alkyl of 1 to 8
7 carbon atoms, phenyl, or benzyl, or one of $R^{8'}$ and $R^{9'}$ is hydrogen and the
8 other is $-\text{COR}^{10'}$, $-\text{SO}_2\text{R}^{10'}$, or $-\text{NHCOR}^{10'}$, or $R^{8'}$ and $R^{9'}$ taken together are
9 tetramethylene, pentamethylene, hexamethylene, or
10 $-\text{CH}_2\text{CH}_2\text{X}^2\text{CH}_2\text{CH}_2-$ in which X^2 is $-\text{O}-$, $-\text{S}-$ or $-\text{NH}-$;

11 R^{10} is hydrogen, alkyl of 1 to 8 carbon atoms, or phenyl; and

12 $\text{R}^{10'}$ is hydrogen, alkyl of 1 to 8 carbon atoms, or phenyl; and

13 (b) the acid addition salts of said compounds which contain a nitrogen atom
14 susceptible of protonation.

15 2. A sulfone according to claim 1 wherein in said compound, Y is $\text{C}=\text{O}$.

16 3. A sulfone according to claim 1 wherein in said compound, Y is CH_2 .

17 4. A sulfone according to claim 1 wherein in said compound, each of R^1 , R^2 , R^3 , and R^4 ,
18 independently of the others, is hydrogen, halo, methyl, ethyl, methoxy, ethoxy, nitro,
19 cyano, hydroxy, or $-\text{NR}^8\text{R}^9$ in which each of R^8 and R^9 taken independently of the other
20 is hydrogen or methyl, or one of R^8 and R^9 is hydrogen and the other is $-\text{COCH}_3$.

- 1 5. A sulfone according to claim 1 wherein in said compound, one of R¹, R², R³, and R⁴ is -
2 NH₂ and the remaining of R¹, R², R³ and R⁴ is hydrogen.
- 3 6. A sulfone according to claim 1 wherein in said compound, one of R¹, R², R³, and R⁴ is
4 -NHCOCH₃ and the remaining of R¹, R², R³, and R⁴ is hydrogen.
- 5 7. A sulfone according to claim 1 wherein in said compound, one of R¹, R², R³, and R⁴ is
6 methyl and the remaining of R¹, R², R³, and R⁴ is hydrogen.
- 7 8. A sulfone according to claim 1 wherein in said compound, one of R¹, R², R³ and R⁴ is
8 fluoro and the remaining of R¹, R², R³ and R⁴ is hydrogen.
- 9 9. A sulfone according to claim 1 wherein in said compound, each of R⁵ and R⁶,
10 independently of the other, is hydrogen, methyl, ethyl, propyl, methoxy, ethoxy,
11 propoxy, cyclopentoxy, or cyclohexoxy.
- 12 10. A sulfone according to claim 1 wherein in said compound, R⁵ is methoxy and R⁶ is
13 ethoxy.
- 14 11. A sulfone according to claim 1 wherein in said compound, R⁷ is hydroxy, methyl,
15 ethyl, phenyl, benzyl, or NR⁸R⁹ in which each of R⁸ and R⁹ taken independently of the
16 other is hydrogen or methyl.
- 17 12. A sulfone according to claim 1 wherein in said compound, R⁷ is methyl, ethyl, phenyl,
18 benzyl, or NR⁸R⁹ in which each of R⁸ and R⁹ taken independently of the other is
19 hydrogen or methyl.
- 20 13. A sulfone according to claim 1 wherein in said compound, R⁷ is methyl.

- 1 14. A sulfone according to claim 1 wherein in said compound, R^7 is $NR^{8'}R^{9'}$ in which each
2 of $R^{8'}$ and $R^{9'}$ taken independently of the other is hydrogen or methyl.
- 3 15. A sulfone according to claim 1 which is 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-
4 sulfonylethyl]isoindolin-1-one, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-(N,N-dimethyl-
5 aminosulfonyl)ethyl]isoindolin-1-one, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-
6 sulfonylethyl]isoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-sul-
7 fonylethyl]-5-nitro-isoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methyl-
8 sulfonylethyl]-4-nitroisoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-meth-
9 ylsulfonylethyl]-4-aminoisoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-
10 methylsulfonylethyl]-5-methylisoindoline-1,3-dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-
11 2-methylsulfonylethyl]-5-acetamidoisoindoline-1,3-dione, 2-[1-(3-ethoxy-4-
12 methoxyphenyl)-2-methylsulfonylethyl]-4-dimethylaminoisoindoline-1,3-dione, 2-[1-(3-
13 ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-5-dimethylaminoisoindoline-1,3-
14 dione, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]benzo[e]isoindoline-
15 1,3-dione, or 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-meth-
16 oxyisoindoline-1,3-dione.
- 17 16. The method of reducing undesirable levels of $TNF\alpha$ in a mammal which comprises
18 administering thereto an effective amount of a compound according to claim 1.
- 19 17. The method of inhibiting PDE IV in a mammal which comprises administering thereto
20 an effective amount of a compound according to claim 1.

- 1 18. A pharmaceutical composition comprising a quantity of a compound according to
- 2 claim 1 sufficient upon administration in a single or multiple dose regimen to reduce
- 3 levels of $\text{TNF}\alpha$ in a mammal in combination with a carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/24376

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/4035, 31/425; C07D 209/46, 209/48, 209/56, 275/06

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/309, 372, 373, 411, 416, 417; 546/41; 548/209, 210, 451, 472, 478

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,556,673 A (ANDERSEN et al.) 03 December 1985, see entire document, especially column 1.	1-18
A	US 5,236,917 A (DUNLAP et al.) 17 August 1993, see entire document, especially columns 4 and 5.	1, 4-14, 16-18
A	US 5,658,940 A (MULLER et al.) 19 August 1997, see entire document, especially columns 4-6.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 DECEMBER 1999

Date of mailing of the international search report

07 FEB 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/24376

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/24376

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/309, 372, 373, 411, 416, 417; 546/41; 548/209, 210, 451, 472, 478

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-18, drawn to compounds of the formula in claim 1 wherein Y represents C(=O), CH₂, or CH₂c(=O), composition and method of use.

Group II, claim(s) 1, 4-14 and 16-18, drawn to compounds of the formula in claim 1 wherein Y represents SO₂, composition and method of use.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: there is a lack of unity among the above identified groups because there is no significant structural element shared by all of the alternatives. Each of the groups set forth above represents a separate discrete heterocyclic ring system which one skilled in the art which beside sharing no significant structural element, cannot be said to belong to a recognized class of chemical compounds in the pharmaceutical art. The claims are therefore considered to lack unity of invention.